Trust Guideline for the Management of: Adult patients requiring anticoagulation with Warfarin (including reversal)

A Clinical Guideline recommended for use:

For Use in:	All Clinical Areas
By:	All medical and nursing staff
For:	Adult patients, aged 16 years and over, requiring anticoagulation with warfarin
Division responsible for document:	Medical Division
Key words:	Warfarin, Anticoagulation initiation, target INR, reversal, Beriplex, Octaplex, Prothrombin Complex Concentrate (PCC)
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If Yes - does the strategy/policy deviate from the recommendations of NICE? If so why?	N/A

This guideline has been approved by the Trust's Clinical Guidelines Assessment Panel as an aid to the diagnosis and management of relevant patients and clinical circumstances. Not every patient or situation fits neatly into a standard guideline scenario and the guideline must be interpreted and applied in practice in the light of prevailing clinical circumstances, the diagnostic and treatment options available and the professional judgement, knowledge and expertise of relevant clinicians. It is advised that the rationale for any departure from relevant guidance should be documented in the patient's case notes.

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Version and Document Control:

Date	Updated version	Previous version	Page number/ section	Details
Aug 2013	V7	V6	E	Doses of PCC removed link to Trust Doc ID 413 inserted
			G	New section added 'head injury on warfarin'
			H	Discharge process clarified
Feb 2014	V7.1	V7	B	Decision process for schedule choice clarified with flow diagram Table headings altered for clarification Table 5 simplified
			C	Table 8 dose of Vitamin K for major bleeding changed from 5mg to at least 5 mg (maximum 10mg)
			F	Dose of Vitamin K for urgent surgery changed from 5mg to at least 5 mg (maximum 10mg)
July 2014	V 7.2	V7.1	H	Discharge arrangements updated (p15) Emergency reversal updated (p11-13) Minor text and formatting revisions Duration table updated (p4)
Oct 2017	V 8.1	V7.2		Authors updated Minor change algorithm pg 3 Minor change to table pg 6 Minor changes to table Page 10 Section D. Page 15. Algorithm removed as no longer current practice
Oct 2017	V8.2	V8.1		Name amended on Trustdocs as Dr Lyall has said he would review as authors have both left the Trust
Nov 2017	V9	V8.2		Approved at Thrombosis and Thromboprophylaxis Committee
March 2021	V10	V9	H	Updated to include EPMA process Key names amended

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Trust Guideline for the Management of:
Adult patients requiring anticoagulation with Warfarin

Abbreviations	
AF	Atrial Fibrillation
DVT	Deep Vein Thrombosis
FFP	Fresh Frozen Plasma
INR	International Normalised Ratio
IV	Intravenous
IVC	Inferior Vena Cava
PCC	Prothrombin Complex Concentrate
PE	Pulmonary Embolism
VTE	Venous Thromboembolism

Objective of Guideline

This guideline applies to patients who require anticoagulation with warfarin or other related Vitamin K antagonists. It aims to standardise anticoagulant management and reversal across the trust in line with national guidelines and in so doing to minimise morbidity and mortality from thrombosis or haemorrhage.

Rationale for Recommendations

These guidelines have been based on the British Committee for Standards in Haematology (BSCH) guidelines.[1]

Introduction

When making the decision to anticoagulate, consideration must be given to the risks of both thrombosis and haemorrhage. Arrangements must be made for the safe monitoring of the patient[2].

Warfarin and other related vitamin K antagonists (coumarins) act by reducing the levels of functional clotting factors II, VII, IX and X. It takes several days to achieve therapeutic anticoagulation. Similarly, when warfarin is discontinued it may take several days for normal haemostasis to be resumed.

Warfarin and other related vitamin K antagonists can be actively reversed with Vitamin K. Most of the anticoagulant effect of warfarin is reversed within 6 hours of an intravenous dose of phytomenadione (vitamin K) or within 24 hours of an oral dose. Patients with major haemorrhage or those needing emergency surgery may require more rapid reversal. In this situation a Prothrombin Complex Concentrate (PCC) such as Beriplex or Octaplex should be used in addition to Vitamin K.

There is now no place for fresh frozen plasma (FFP) for the reversal of Warfarin.
In massive haemorrhage associated with warfarin FFP and a source of fibrinogen may be required in addition to PCC and Vitamin K to replace other coagulation factors which have become depleted (see trust guideline Trustdocs ID 1175
Massive Blood Loss in adults')

Pharmaceutical preparations

2 tablet sizes are used in the NNUH: - 3mg (Blue tablets)
1mg (Brown tablets)

It is also available in 5mg (Pink) and 0.5mg (White) tablets but these are not stocked or used at the NNUH. NB. If patient has their own supply they can self-medicate using their own tablets.

Section A Target INR and Duration of anticoagulation

NB. The term 'target INR' and 'target range' are used interchangeably. The target range is the target INR +/- 0.5 INR units e.g. for a target INR of 2.5 the target range is 2.0 – 3.0.

VTE (DVT and/or PE) - based on BCSH recommendations (2011 update of guidelines on oral anticoagulation (4th edition)[1]

Indication	Target INR	Minimum duration
Calf – irrespective of risk factor	2.5	6/52
proximal DVT or PE – temporary risk factor	2.5	3/12
proximal DVT or PE - idiopathic or permanent risk factor	2.5	3/12 consider lifelong
VTE associated with Antiphospholipid syndrome	2.5	while disease active consider lifelong
Recurrence of VTE *while on* Warfarin in therapeutic range	3.5	lifelong
Recurrence of VTE *after* cessation of warfarin	2.5	review for permanent risk factors ? lifelong
Cancer with VTE	2.5 consideration for therapeutic LMWH as an alternative or DOAC	6 months. Consider longer if cancer remains active

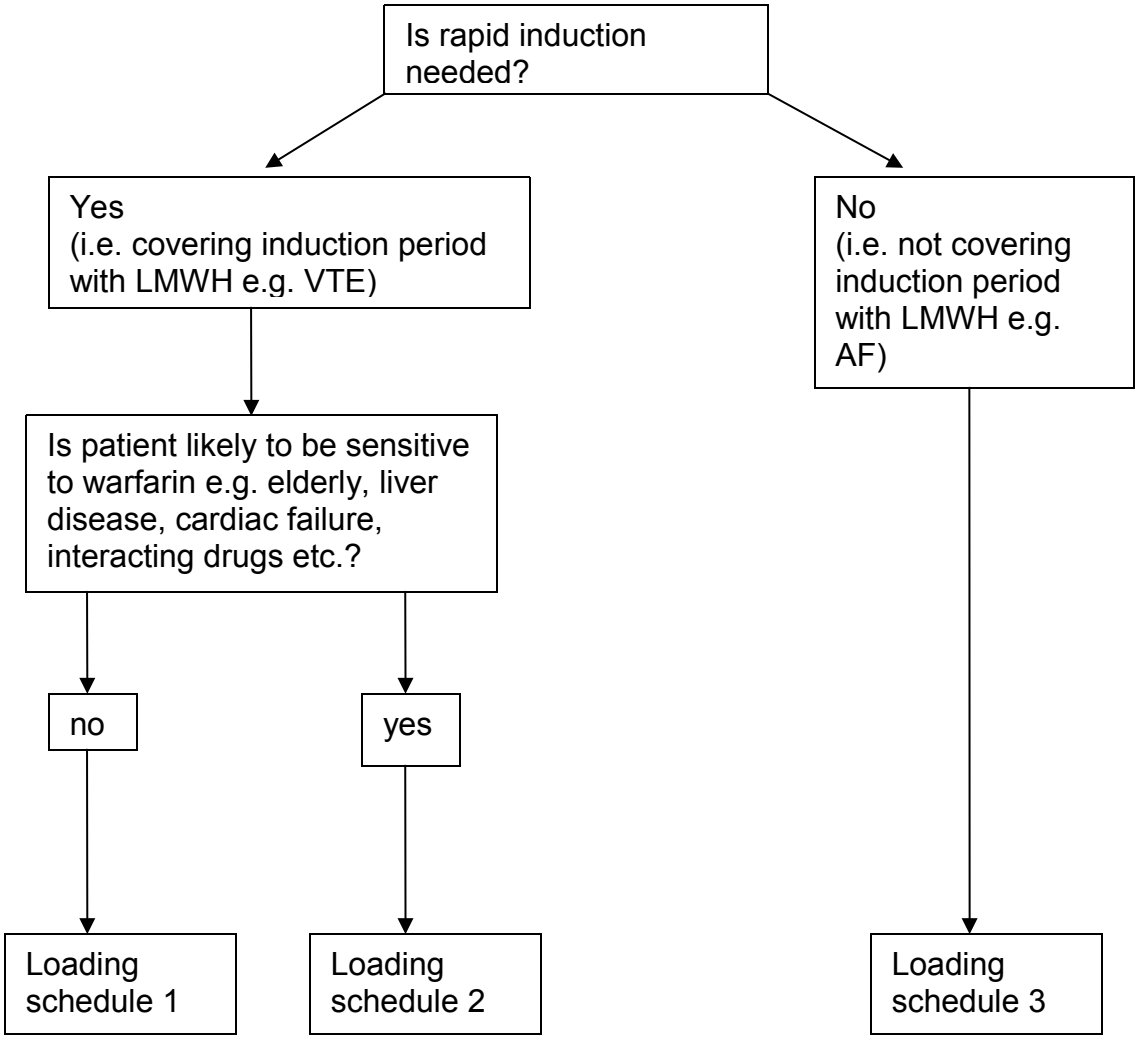
Cardiac Indications based on Papworth guidelines for valve replacements

Indication	Target INR	Minimum duration
Atrial Fibrillation	2.5	Lifelong *unless* for cardioversion
Cardioversion	2.5	Should be in *therapeutic range* (2-3) for at least 4 wks before and 4 weeks after cardioversion
Mural thrombus	2.5	3/12
Mechanical heart valve	2.5 or 3.0 or 3.5 (as per cardiologist advice)	lifelong
Bioprosthetic (tissue) valve	None unless specified	None unless specified

Other

Indication	Target INR	Minimum duration
Arterial thrombosis associated with anti-phospholipid syndrome	2.5	while disease active ? lifelong
Peripheral arterial thrombosis and grafts	2.5	long term
Paroxysmal Nocturnal Haemoglobinuria	2.5	long term

Section B Induction regimens



Warfarin loading schedule 1 (Fennerty 1988[3])

Table 1 Warfarin loading schedule 1 - Days 1 to 4

Day	*INR Result*	*Warfarin Dose*	*Follow up*
1	*If INR <1.4*	*10mg*	*Next INR Day 3*
2	*ND*	*10mg*	*as above*
3	*< 2.0*	*10mg*	*Next INR Day 4*
	2.0 – 2.3	*5mg*	
	2.4 – 2.7	*4mg*	
	2.8 – 3.1	*3mg*	
	3.2 – 3.4	*2mg*	
	3.5 – 4.0	*1mg*	
	> 4.0	*omit*	
4	*< 1.4*	*12mg*	***see loading schedule (Table 2) from day 4 below***
	1.4	*8mg*	*Next INR Day 6 ** *
	1.5	*8/7 mg alt days*	
	1.6 – 1.7	*7mg*	
	1.8	*7/6 mg alt days*	
	1.9	*6mg*	
	2.0 – 2.3	*5 mg*	*Next INR Day 5**
	2.4 – 3.0	*4mg*	
	3.1 – 3.5	*3/4mg alt days*	*Next INR Day 6**
	3.6 – 4.0	*3mg*	
	4.1 – 4.5	*omit day 4*	*next INR Day 5 and then daily; once INR <3.5 restart Warfarin at 3mg*
	> 4.5	*omit for 2 days i.e. day 4 and 5*	*next INR Day 6 and then daily; once INR <3.5 restart Warfarin at 3mg*

** *INR **in range** continue with dose - follow up by GP*
*INR **not in range** see Table 6 or Table 7 for suggested dose*

Table 2 Warfarin loading schedule 1 - from day 4 for patients with INR <1.4 on day 4

Day	INR	Warfarin Dose	Follow up
4	< 1.4	12mg for 2 days	next INR day 6
6	> 2.0 <3.0	12 mg	by GP day 8 – 10; if >3.0 see table 7
	< 2.0	14mg for 2 days	next INR day 8
8	> 2.0 <3.0	14 mg	by GP day 10 – 12; if >3.0 see table 7
	< 2.0	16mg for 2 days	next INR day 10
10	> 2.0 <3.0	16 mg	by GP day 12 – 14; if >3.0 see table 7
	< 2.0	**see table 6 for suggested dose**	

Warfarin loading schedule 2 (Norwich 2009)

This Warfarin loading schedule should be considered for patients

- with high risk factors such as congestive cardiac failure, liver disease, intercurrent illness
- taking other drugs known to potentiate Warfarin
- over 75 years

N.B These patients are more likely to encounter problems with warfarin.
A review of risk: benefit ratio of anticoagulation should be considered

Table 3 Warfarin loading schedule 2

Day	INR	Warfarin Dose	Follow up
1	<1.4	10mg	Next INR day 2
2	<1.2	3mg	Next INR day 3
	1.2 – 1.5	2mg	
	1.6 – 2.0	1mg	
	2.1 – 2.4	omit	
	>2.5	omit	Seek medical advice
3	<2.0	4mg	Next INR day 4
	2.0 – 2.5	2mg	
	2.6 – 2.9	1mg	
	3.0 -3.5	omit	
	>3.5	omit	
4	<1.4	9mg	INR day 6 - if INR in range continue same dose – follow up by GP - if INR not in range **see table 6 or 7 for suggested dose**
	1.4 – 1.5	7mg	
	1.6 – 1.7	6mg	
	1.8 – 1.9	5mg	
	2.0 – 2.3	3mg	INR day 5 - if INR in range continue same dose – follow up by GP - if INR not in range **see table 6 or 7 for suggested dose**
	2.4 – 3.0	2mg	
	3.1 - 3.2	2mg	INR day 6 - if INR in range continue same dose – follow up by GP - if INR not in range **see table 6 or 7 for suggested dose**
	3.3 – 3.5	1mg	
	3.6 – 4.0	omit	INR daily - once INR < 3.5 restart Warfarin at 2mg.
	> 4.0	omit 2 days	Next INR day 6 - once INR < 3.5 restart Warfarin at 2mg

Warfarin loading schedule 3 (Janes 2004)[4]

For patients with atrial fibrillation not requiring rapid anticoagulation (i.e. patients not requiring heparinisation)

Ensure INR is <1.4 before treatment. If INR >1.4 consider reasons for raised INR and consider if warfarin definitely indicated

Start Warfarin 3 mg po daily at 6 pm

unless patient frail, is on amiodarone or has impaired liver function – ALT >=2 x upper limit of normal when use a starting dose of warfarin 2mg po daily at 6pm
Continue this dose of warfarin (2mg or 3mg daily) until day 8 when INR should be checked. See table 4 for loading schedule 3 from day 8. If patient is an inpatient or there any concerns about overanticoagulation then check INR sooner than stated.

Table 4 Warfarin loading schedule 3 at day 8

Day	INR	Starting dose 3mg Warfarin Dose	Starting dose 2mg Warfarin Dose	Follow up
8	<1.4	6mg	5mg	INR 1 week (day 15) - see table 5
	1.4 –1.5	5 mg	4 mg	Check INR 1 week **INR** **Warfarin** 2-3 Present dose >3 Table 7 <2 Table 6
	1.6 – 1.8	4 mg	3 mg	
	1.9 – 2.1	3 mg	2 mg	
	2.2 – 2.5	2.5 mg	1.5 mg	
	2.6 – 2.7	2 mg	1 mg	
	2.8 – 3.0	Omit 2 days; 1mg	omit 2 days; 1mg	
	>3.0	Stop	Stop	Recheck INR 3-5 days restart at 1mg if INR < 2.5 and warfarin definitely indicated; recheck again in 2 days - if INR 2-3 continue present dose otherwise see Table 6 or 7

Table 5 loading schedule 3 Warfarin dosing day 15 for patients *INR <1.4 on day 8*

Day	INR	Current dose = 6mg Warfarin	Current dose = 5mg Warfarin	Follow up
15	<1.4	10 mg – check compliance	10mg check compliance	Check INR 1 week **INR** **Warfarin** 2-3 current dose >3 Table 7 <2 Table 6
	1.4-1.5	8mg	7mg	
	1.6-1.8	7mg	6mg	
	1.9-2.4	6mg	5mg	
	2.5-2.9	5mg	4mg	
	>3	See table 7	See table 7	

Section C Patient underanticoagulated

Table 6 shows suggested % increase in daily Warfarin dose**.** The dose should be rounded ***up*** to nearest 0.5mg - **tablets should not be broken** e.g. if suggested dose 1.5mg daily give 2mg/1mg alternate days **start with higher dose** i.e. 2mg

Table 6 Patient Underanticoagulated

INR	Target INR	Increase dose by %	* suggested increase for medically unstable patients
<1.0 – 1.2	2.5	30%	15%
	3.0	35%	20%
	3.5	40%	25%
1.3 – 1.5	2.5	25%	10%
	3.0	30%	15%
	3.5	35%	20%
1.6 – 1.9	2.5	20%	5%
	3.0	25%	10%
	3.5	30%	15%
2.0 - 2.4	3.0	20%	5%
	3.5	25%	10%
2.5 - 2.9	3.0	10%	NA
	3.5	20%	5%
3.0 - 3.4	3.5	10%	NA

*If the patient is medically unstable i.e. requiring frequent changes in medication or management 15% can be subtracted from the suggested increase dose change (i.e. 20% would be 5%)

Repeat INR 2-3 days later (it will take **at least 2 days for any change in dose to have full effect**) or sooner if clinically indicated e.g. active bleeding or medically unstable, in which case check next day

Section D Patient overanticoagulated

Table 7 Patient overanticoagulated INR <8, NOT bleeding

Table shows suggested % decrease in daily Warfarin dose**.** The dose should be rounded ***down*** to nearest 0.5mg – **tablets should not be broken** e.g. if suggested dose 1.5mg daily give 1mg/2mg alternate days **start with lower dose** i.e. 1mg.

Target INR 2.5			
INR	**omit Warfarin days**	**Repeat INR**	**Suggested % dose reduction once Warfarin restarted***
3.1-3.5	0	at 2 days unless clinically indicated e.g. active bleeding or medically unstable	15
3.6-4.0	0	at 2 days unless clinically indicated e.g. active bleeding or medically unstable	20
4.1-5.0	1 day	at 1 day unless clinically indicated e.g. active bleeding or medically unstable	25
5.1-6.0	at least 1	daily restart Warfarin once INR <3.5	25
6.1-7.9	at least 2	daily restart Warfarin once INR <3.5	33
>8.0	see table 8	daily; **ward medical staff must be informed and involved in management**	50
Target INR 3.0			
3.6-4.0	0	at 2 days unless clinically indicated e.g. active bleeding or medically unstable	15
4.1-5.0	1 day	at 1 day unless clinically indicated e.g. active bleeding or medically unstable	20
5.1-6.0	at least 1	daily restart Warfarin once INR <4.0	25
6.1-7.9	at least 2	daily restart Warfarin once INR <4.0	33
>8.0	see table 8	daily; **ward medical staff must be informed and involved in management**	50
Target INR 3.5			
4.1-5.0	0; *unless* patient medically unstable when omit dose	at 2 days unless clinically indicated e.g. active bleeding or medically unstable	15
5.1-6.0	1 day	at 1 day unless clinically indicated e.g. active bleeding or medically unstable	20
6.1-7.9	at least 2	daily restart Warfarin once INR <4.5	33
> 8.0	see table 8	daily; if not already **ward medical staff must be informed and involved in management**	50

****If the patient is medically unstable up to 15% can be added to the suggested dose reduction (i.e 10% would be 25%) or if the precipitating cause has been identified and removed/stopped (e.g. interacting drugs) up to 15% may be subtracted (i.e. 20% would be 5%)***

Table 8 INR >8 or major bleeding	
INR	**Action**
INR >8.0, no bleeding or minor bleeding	• stop Warfarin • give 2mg of phytomenadione orally (vitamin K; use iv Konakion MM preparation orally) • recheck INR daily • try to identify precipitating cause - is it temporary e.g. drug or permanent e.g. liver failure? • if INR still >8 at 24 hours consider repeating dose of phytomenadione • when INR <5, review need for anticoagulation • restart Warfarin if appropriate at reduced dose - 50% of previous dose
Major bleeding - defined as haemorrhage with hypovolaemic shock *or* bleeding into a confined space - • intracranial • intraocular • compartment syndrome • pericardial	• stop Warfarin • urgent clinical assessment • urgent clotting screen • give 5-10 mg phytomenadione (vitamin K) intravenously • give prothrombin complex concentrate (obtained from Blood bank) • check clotting screen 1 hr after administration **inadequate correction**: discuss with consultant haematologist • recheck INR within 24 hours and daily thereafter • treat source of bleeding • review need for anticoagulation before restarting • restart Warfarin if appropriate at reduced dose - 50% of previous dose

Notes

- some patients who require interruption of anticoagulation may require insertion of temporary IVC filter (see Trust guideline Trustdocs Id:1252) on insertion of vena cava filters) e.g. with very recent PE who require emergency surgery
- all patients should have their indications for anticoagulation reviewed prior to restarting warfarin and the risks of thrombosis versus further bleeding assessed
- incident forms should be completed for patients who develop INRs > 8 while hospital in-patients or who are admitted to hospital as a result of overanticoagulation

Section E Prothrombin Complex Concentrate (Beriplex/Octaplex)

See Trust document Prothrombin Complex Concentrate for dosing and administration instructions

General information

- derived from human plasma (i.e. it is a blood product)
- contains coagulation factors II, VII, IX and X, but no other procoagulant factors
- kept in Blood Bank as a freeze-dried powder which is reconstituted with a small volume of water just prior to use
- given by slow IV injection. See advice sheet Prothrombin Complex Concentrate
- doses given are based on the dose of administered factor IX

Indications

Patients anticoagulated with warfarin or other vitamin K antagonists e.g. phenindione who:

- have major haemorrhage (N.B. all coagulation factors may eventually decline and FFP +/- source of fibrinogen may also be required)
- have haemorrhage into a critical site e.g. intracranial, intraocular, pericardial, muscle bleed with compartment syndrome
- require surgery within 6 hours

Contraindication

- caution in patients who have had venous thromboembolism within last month (Prothrombin Complex Concentrate is thrombogenic).
- contraindicated in patients known to be allergic to Beriplex or Octaplex

Possible side effects

- thrombosis
- disseminated intravascular coagulation (DIC)
- allergic reactions
- although product has viral safety measures employed during manufacture the risk of transfusion transmitted infection should still be considered

Section F Surgical patients on Warfarin

- **Emergency surgery within 6hours** – give Prothrombin Complex Concentrate Beriplex/Octaplex (see Prothrombin Complex Concentrate advice sheet) **and** phytomenadione 5-10 mg by slow IV injection. Check INR pre operatively.
- **Emergency surgery within 6- 24 hours** – give phytomenadione 5-10 mg by slow IV injection; check INR pre operatively (at least 6 hours post Vitamin K). If INR not corrected (i.e. INR result > 1.5) discuss with haematologist.
- **Emergency surgery >24 hours** – give phytomenadione 5-10 mg by slow IV injection (or orally if absorption not impaired). Check INR pre operatively. Consider administering an alternative anticoagulant for 'bridging anticoagulation' if there is going to be a significant interval between reversing warfarin and surgery (generally if surgery > 24 hours post reversal) and high thrombotic risk.
- **Elective surgery:** see Adult patients on therapeutic anticoagulation who require elective surgery or an invasive procedure. Trustdocs Id:1215.

Additional notes

- some patients who require interruption of anticoagulation may require insertion of a temporary IVC filter (see Insertion of Vena Cava Filters Trust guideline Trustdocs Id:1252) e.g. with venothromboembolism within the last month who require emergency surgery.
- review indication for warfarin before restarting postoperatively. Consider if an alternative anticoagulant is required in the post-operative period whilst warfarin is subtherapeutic. Refer to **Trust guideline** Trustdocs Id:1215 **'**Adult patients on therapeutic anticoagulation who require elective surgery or an invasive procedure' for advice on post-operative management.

Section G Head injury in patients on warfarin

Recommendations adapted from BCSH guidelines 4th edition 2011

- All patients on warfarin presenting with head injury should have their INR measured as soon as possible
- A lower threshold for performing a head CT scan should be used for patients on warfarin
- Patients on warfarin presenting with a strong suspicion of intracerebral bleed should have their anticoagulation reversed before the results of any investigations

Section H Discharge of Patients on Warfarin

On discharge

- The anticoagulation nurse specialist (ANS) **must** be contacted **prior** to discharge to ensure appropriate warfarin dosing and follow up arrangements for INR monitoring are made (ext. 3809 bleep 0799/0918).
- The anticoagulant nurse specialists run a seven day week service (Daily 08.30-18.00, excluding Christmas day and New Year's day).
- All patients who commenced warfarin this admission (i.e. were not taking warfarin prior to admission) must be counselled regarding the risks and benefits of anticoagulation. They must also be issued with the national anticoagulation therapy pack (previously known as the 'yellow book').
- All patients should have their anticoagulation therapy record (yellow book) updated prior to discharge. Where this is not possible print the TTO list from EPMA with the patients dosing information.
- All patients must be prescribed and issued with Warfarin (1mg and 3 mg tablets) and LMWH (if needed) on the TTOs

* If patients are discharged unexpectedly out of ANS working hours a message must be left with the anticoagulation nursing team on answerphone (3809). If any concerns the ANS will liaise directly with the discharging ward.

Clinical Audit Standards derived from this guideline

Anticoagulant monitoring follows these guidelines

Management of Warfarin over dosage follows these guidelines

Discharge of patients on anticoagulants follows these guidelines

Appropriate choice of target INR; duration of anticoagulation

Management of high INRs

Summary of development and consultation process undertaken before registration and dissemination

This guideline was drafted by the authors and reviewed by all consultant haematologists; all members of the Thrombosis and Thromboprophylaxis Committee and Thrombosis committee, appropriate comments and amendments from the above have been incorporated.

Distribution list / dissemination method

This guideline will be available on the trust intranet.

References

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